REMARKS

Reconsideration is respectfully requested. Claims 20, 22, 23, and 30-39 are pending. Claims 1-19, 21 and 24-29 have been canceled. Amendments to the claims do not add new matter and do not affect the inventorship.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claims Rejection - 35 U.S.C. § 112, First Paragraph

Claims 20, 22, 23, and 30-39 stand rejected under 35 U.S.C. 112, first paragraph, for alleged new matter. Applicants respectfully disagree.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Claims 20 and 30 require:

> [A] passivation agent monolayer comprising at least a covalently attached first passivation species and a covalently attached second passivation species comprising a protein binding ligand.

There is ample description in the specification. For example, the specification discloses a passivation agent monolayer at page 34, lines 10-19 ("the electrode further comprises a passivation agent, preferably in the form of a monolayer on the electrode surface"), that comprises two species, at page 35, lines 28-29 ("The monolayer may comprise a single type of passivation agent, including insulators, or different types"), page 37, lines 31-33 ("electrodes may be made that have any combination of components. Thus, a variety of different conductive oligomers or passivation agents may be used on a single electrode"), and page 34, lines 24-27 ("the passavation agents themselves may in fact be either (1) conducting or (2) nonconducting, i.e. insulating, molecules. Thus, in one embodiment, the passavation agents are conductive oligomers, as described herein, with or without a terminal group to block or decrease the transfer of charge to the electrode.")

Applicants would also like to draw Examiner's attention to the drawings on pages 14-16 and 18-20, depicting a variety of systems where one or more species of passivation agents forming monolayer on the surface of an electrode. For example, the instant application discloses on page 21, lines 1-6 that:

> In a preferred embodiment, the redox active molecule will be attached via a conductive oligomer.... Other components of the system may be attached using other spacers; for example, when the binding ligand and the redox active molecule are attached separately, as is generally depicted in System 2, the binding ligand may be attached via a non-conductive oligomer spacer. (Emphasis added).

Therefore, System 2 depicts at least two species of passivation agents forming monolayer on the surface of an electrode, where one species is "a conductive oligomer" attached to a redox active molecule and the other species is "a non-conductive oligomer spacer" attached to a binding ligand.

The specification also discloses that the passivation agents are attached to the electrode covalently. See page 37, lines 16-18 ("a monolayer of passivation agents is added to the electrode. Generally, the chemistry of addition is similar to or the same as the addition of conductive oligomers to the electrode, i.e. using a sulfur atom for attachment to a gold electrode, etc.,") and page 14, lines 10-13, ("F1 is a linkage that allows the covalent attachment of the electrode and the conductive oligomer or insulator, including bonds, atoms or linkers such as is described herein, for example as "A", defined below" (emphasis added)).

The instant application also discloses passivation species comprising a protein binding ligand. See page 11, lines 8-10 ("when the analyte is a protein, the binding ligands include proteins (particularly including antibodies or fragments thereof (FAbs, etc.))"), page 20, lines 29-20 ("the binding ligand [is] attached, via a spacer, to the electrode"), page 21, line 8 ("the spacer is a conductive oligomer,") page 21, lines 5-6 ("the binding ligand may be attached via a non-conductive oligomer spacer.")

Therefore, contrary to the Examiner's contention, the specification has ample support for two different covalently attached passivation species in the same monolayer that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. Accordingly, Applicants respectfully request the rejection be withdrawn.

Claims Rejection - 35 U.S.C. § 103

I. Claims 20, 30, 34 and 36

Claims 20, 30, 34 and 36 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hollis et al. (WO 93/22678) ("*Hollis*") in view of *Agladze* (Metallurgy and Foundry Engineering (1997) 23(2), 127-137) ("*Agladze*"). Applicants respectfully traverse.

1) The *Graham* Factors

When rejecting claims under 35 U.S.C. §103, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142. The inquiry of obviousness is controlled by the *Grahm* factors. See *KSR International Co. v. Teleflex Inc.* 1727 S.C.t (2007) (citing *Graham v. John Deere Co. of* Kansas *City*, 383 U.S. 1 (1966)). These factors are: 1) the scope and content of the prior art; 2) the differences between the prior art and the claims; 3) the level of ordinary skill in the pertinent art; and 4) objective evidence of nonobviousness.

A. *Hollis*

Hollis is directed to method and apparatus for identifying molecular structures within a sample substance. *Hollis* does not teach or suggest "a passivation agent monolayer."

The Examiner correctly notes that *Hollis* teaches microarrays and passivation layers. However, any similarity between *Hollis* and the instant invention ends there. For example, *Hollis* teaches a "glue" layer under a SiO_2 or Si_3N_4 passivation layers, which glue layer is exposed through discriminate ablation of the passivation layer. See, e.g., pg. 29, lines 5-7 and Figure 26. Thus, the net effect of ablation is elimination of the passivation layer at the point of ligand attachment—something *antithetical* to the merit of the instant claims, which are directed to a monolayer comprised of two passivation species, one of which is attached to a protein binding ligand.

The Examiner incorrectly asserts that *Hollis* discloses "upper and lower electrodes covered with a film" at page 11, lines 14-32. *Hollis* does not disclose any film on the electrodes. The only "film" disclosed at this reference is a film of Si_3N_4 which is under the upper electrode.

The Examiner asserts that the apparatus of *Hollis* includes "a passivation agent monolayer." *Hollis* discloses a passivation layer which is not a monolayer. *Hollis* states "[t]he wells are passivated with a thin protective layer (not shown), such as silicon nitride or aluminum oxide to prevent degradation of the CCD device due to exposure to aqueous solution." Page 20, lines 16-19. On page 29, lines 13-16 *Hollis* states "[p]assivating materials can be hydrophobic materials such as fluorine-terminated fluorocarbons or the derivatives or hexamethyldisilizane." There is no other description of a passivation layer in *Hollis*.

In the first example from *Hollis* the passivation layer is formed over a CCD device, not on measuring electrodes as in the present invention. Further, the "protection layer" of *Hollis* is composed of silicon nitride or aluminum oxide which are amorphous materials and is not monolayer.

In the second example from *Hollis*, the "passivating materials" are used to cover portions of a "glue" layer, not an electrode as in the present invention. Suggested materials are fluoramine-terminated fluorocarbons or the derivatives of hexadimethyldisilizane." Such passivating materials do not form monolayers over the glue layer.

As the Examiner notes, *Hollis* describes a passivation layer on the electrodes at page 44, lines 6-9: "[a]lthough the method of detection will withstand some corrosion of the electrodes, a passivation layer can be employed to coat the plates for even longer use." The Examiner notes that "Applicant has acknowledged that Hollis describes a passivation layer on the electrodes." However, as the Examiner can appreciate, a "layer" is not the same as a "monolayer," and the latter is what recited by the claims. The Examiner also notes that "because Hollis teaches electrode coating procedures to form passivation layers and such coating read on monolayer preparations." Office Action dated 04-18-07, page 11. However, as the Examiner can appreciate, "layer" is a genus, and "monolayer" is a species. "A genus does not always anticipate a claim within the genus." MPEP 2131.02. This example of the use of a passivation layer is different from the above where the layer coats a CCD device or a glue layer. *Hollis* does not indicate what this passivation layer is composed of and does not describe the use of a monolayer at any point in the patent application.

B. *Agladze*

(1) *Agladze* is non-analogous art.

The Examiner cites *Agladze* for the proposition that "passivation films (layer) can modified [sic] electrode reactivity reactions via OH ions (species one) and anions (species two)." Applicant submits that *Agladze* is improperly cited as it is not analogous art.

"In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). M.P.E.P. §2141.01(a).

The instant invention is directed to measuring electrodes comprising two passivation agent monolayer species, one of which comprises a protein binding ligand. In stark contrast, the concern of *Agladze*, as indicated by the tile, is about "The Modern Understanding of Corrosion and Passivation

Process of Iron Group Metals." *Agladze* discusses studies in the field of metal corrosion. Therefore, *Agladze* is not in the field of applicant's endeavor.

As for the latter, a reference in a different field from that of the inventor's endeavor may be reasonably pertinent only if "because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re ICON Health and Fitness Inc.*, 83 USPQ2d 1746 (Fed. Cir. 2007) (citing *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992)).

Here the particular problem with which the inventor was concerned is the detection of biological target analytes, utilizing monolayers. Thus a "passivation agent monolayer facilitates the maintenance of the target analyte away from the surface of the electrode." Instant application, page 34, lines 11-14. In *Agladze* the formation of passive film results in retardation of electrode reactions. See page 136, lines 23-24. Specifically *Agladze* discussed the passivation of iron, which logically, would not have commended itself to the attention of an inventor who is interested in measuring electrodes comprising two passivation agent monolayer species, one of which comprises a protein binding ligand. Therefore *Agladze* is not reasonably pertinent to the particular problem with which the inventors are concerned - the efficiency of binding between the target analyte and the binding ligand.

Applicant further notes *Agladze* is related to erosion protection of metal and *Hollis* is concerned with the protection of electrodes from erosion and discloses at page 44, lines 6-9 that "a passivation layer can be employed to coat the plates for even longer use." However, the instant application is not directed to corrosion of an electrode, but rather is directed to the detection of analyte with an electrode. An inventor considering to add to the surface a "passivation agent layer facilitates the maintenance of the target analyte away from the surface of the electrode" and one of the " passivation species comprising a protein binding ligand" would not pay attention to references that dealing with corrosion prevention of metal, such as *Agladze*. This is especially true because electrode of the present invention can be "gold, platinum, and graphite" and, as such, erosion is not a concern.

For the forgoing reasons, *Agladze* is a non-analogous art and should not be cited.

Further, the Applicants did not argue that *Kossovsky* and *Wohlstadt*r are non-analogous art in the previous response as the Examiner alleged on page 13; Applicants respectfully request clarification.

(2) *Agladze* does not complement the deficiencies of *Hollis*.

Applicants further submit, contrary to the Examiner's assertion, *Agladze* does not disclose that the "OH ions and anions" form a monolayer.

The CAS abstract states that "...the formation of primary passive film consisting of adsorbed OH ions and anions results in a strong retardation of electrode reactions..." See also *Agladze*, page 136, lines 23-24. The Examiner makes the assumption that the OH ions and the anions are in the same monolayer. Contrary to the examiner's assumption, *Agladze* compares the differing affect of these different species and studies the species independently of one another. *Agladze* only provides the conjecture that "it is reasonable to assume that the primary passive film consists mainly of adsorbed hydroxide groups and anions adsorbed either according to solvent displacement or hydrogen-bonding mechanisms." Page 132, lines 22-24 (emphasis added). There is no teaching that the species are actually present at the same time. Thus, *Agladze* does not teach "that passivation films (layers) can modified [sic] electrode reactivity reactions via OH ions (species one) and anions (species two)."

Further, "OH ions and anions" do not form "monolayers" as they are taught in the instant application. One of the functions of the monolayer is to keep charge carriers away from the electrode surface; clearly, OH ions and anions are charge carriers.

Moreover, claims of the present invention require that the passivation species of the monolayer be covalently attached. *Agladze* discloses "adsorbed OH ions and anions." The Examiner cites Kaxiras, Materials Research Society Symposium Proceedings, 1999, 193 (At. Scale Calc. Structure Mater.) (*"Kaxiras"*) and Ohno, Surface Science, 1991, 255(3), 229-236 (*"Ohno"*), another two abstracts, and states that "[t]he prior art shown that "adsorption" can produce covalent bonded passivation monolayers." However, there is no disclosure in *Agladze* that the anions and cations form bonds with the metal. In fact, *Agladze* teaches that the adsorbed species are not covalently attached but, rather, are held by physical forces that allow desorption: "The steady-state concentration of surface active sites in this case will be determined by the balance of the rates of reactions of metal dissolution (1', 2'), adsorption and desorption of passivating film." Page 134, lines 29-31 (emphasis added).

2) There is no motivation to combine *Agladze* with *Hollis* to reach the claimed invention

"[A] patent composed of several elements is not proved obviousness merely by demonstrating that each of its elements was, independently, known in the prior art.... [I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, at 1743.

A. There is no motivation to search for *Agladze*.

Agladze teaches metal corrosion prevention in the field of metallurgy. Logically, it would not have prompted a personal skill in the filed of biosensor to combine it with other elements to reach the

claimed invention - measuring electrodes comprising two passivation agent monolayer species, one of which comprises a protein binding ligand. A person of ordinary skill in the art of protein detection would not be motivated to search out techniques regarding corrosion prevention and to combine such techniques in the field of the present invention. Further still, for embodiments of the claimed invention in which the electrode is gold or platinum or graphite coated, it is difficult to see how iron corrosion is even remotely implicated.

Thus, there is no motivation to combine *Agladze* with *Hollis* to reach the claimed invention.

B. *Hollis* teaches away from the claimed invention.

"[W]hen the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR*, at 1740. "[A] reference may teach away when a person skilled in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re ICON*, at 1751.

The present invention requires "passivation species comprising a protein binding ligand." In contrast, *Hollis* discloses the in order to add a probe (i.e. DNA) to the surface the "passivating layer" has to be ablated to expose the "glue layer" under it. See Fig. 26A-26D of *Hollis*. Thus, an inventor, upon reading *Hollis*, would ablate the passivating layer from the surface of the electrode and attach a probe to the glue layer under, not the passivating layer. This is a path opposite to what the Applicants had taken, to have "a passivation agent monolayer comprising ... second passivation species comprising a protein binding ligand."

C. The proposed modification or combination of *Agladze* with *Hollis* would change the principle of operation of *Agladze*.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959), M.P.E.P. § 2143.02 VI.

As presented herein, in *Agladze*, the formation of passive film leads to retardation of electrode reactions to prevent corrosion. See page 136, lines 23-24. In contrast, in the present invention, a "passivation agent layer facilitates the maintenance of the target analyte away from the surface of the electrode." Instant application, page 34, lines 11-14. Thus, combining *Agladze* with *Hollis* would change the principle of operation of *Agladze* – a change from *chemically* retardation of electrode reactions to

physically keeping that target analyte away from the surface of the electrode. Therefore, the teachings of *Agladze* and *Hollis* are not sufficient to render the claims *prima facie* obvious.

D. The proposed modification of *Hollis* would render *Hollis* unsatisfactory for its intended purpose

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), M.P.E.P. § 2143.01 V.

Agladze discloses that "passive film consisting of adsorbed OH ions and anions" serve to protect metal from corrosion. However, *Hollis* discloses the in order to add a probe (i.e. DNA) to the surface the "passivating layer" has to be ablated to expose the "glue layer" under it. See Fig. 26A-26D of *Hollis*. Thus, if one modify *Hollis* by adding the *Agladze* "passive film" on the surface of the electrode and not ablate, one can not expose the glue layer and attach the probe to the glue layer. Thus the electrode would not work for the intended purpose – to detect an analyte.

E. There is no a reasonable expectation of success by combining *Agladze* and *Hollis*.

The Supreme Court also held in *KSR* that, "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, at 1739. Thus evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048 (CCPA 1976). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990). MPEP. § 2143.01.

As presented above, to add the *Agladze* "passive film consisting of adsorbed OH ions and anions" to the surface of the electrode and not ablate the "passive film", one can not expose the glue layer and attach the probe to the glue layer. Thus the electrode could not be used work to detect an analyte. Thus there is not expectation of success by combining *Agladze* and *Hollis*.

II. Claims 31-33 and 37-39

Claims 31-33 and 37-39 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over *Hollis* in view of *Agladze*, and further in view of Kossovsky *et al.* US Patent No. 5,585,646 ("*Kossovsky*"). The rejection is traversed as applied to claims 31-33 and 37-39.

For the reasons set forth previously, *Hollis* and *Agladze* combined do not render the claimed combinations obvious. Further, *Kossovsky* does not overcome the deficiencies because *Kossovsky*, as the

Examiner admits, is directed to polyhydroxide polysaccharide and carbohydrate passivation matrices, the end result of which would be an inability to limit ligand attachment to the external surface and thereby provide a discernable passivation layer separate from the ligand attachment site. As the Examiner notes, *Agladze* teaches the reactivity of polyhyroxides and the possibility for chemical modification thereof. Further, the instant claims contemplate two species of passivation layer, one of which is obligatorily bound to the ligand. *Kossovsky* does not teach or suggest this. Thus, once again, there is not proper motivation to combine the references, and *even combining them* does not result in the claimed invention. Accordingly, the Examiner is respectfully asked to reconsider and withdraw this ground of rejection.

Applicants further notes that the Examiner cites the *Kayyem* reference on page 8 of the instant Office Action even this reference is removed from the rejection. Applicants respectfully request clarification.

III. Claim 35

Claim 35 stands rejected under 35 U.S.C. § 103 (a) as allegedly unpatentable over *Hollis*, in view of *Agladze* and further in view of *Wohlstadter et al.* US Patent No. 6,090,545 ("*Wohlstadter*"). The rejection is traversed as applied to claim 35.

For the reasons set forth previously, *Hollis* and *Agladze* combined do not render the claimed combinations obvious. *Wohlstadter* does not overcome these deficiencies. Accordingly, the Examiner has failed to make a prima facie case, and the references taken alone or combined cannot be said to anticipate or render obvious the claimed invention based on what the Examiner has articulated. For this reason, the instant rejection is respectfully asked to be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 442-1000.

Respectfully submitted,

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